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Acquired Factor VIII Inhibitors—Successful Treatment With an Oral Outpatient Regimen

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A rare cause of a spontaneous, life threatening coagulopathy in adults is the development of autoantibodies to factor VIII. We recently had the opportunity to treat seven patients with this disorder. After stabilization, they were given a regimen consisting of prednisone and oral cyclophosphamide. All patients had a complete response to treatment. The median time to response was three weeks. Durable remissions were achieved, making this oral regimen an acceptable treatment for this disorder. Am. J. Hematol. 60:70–71, 1999. © 1999 Wiley-Liss, Inc.

Key words: factor VIII antibody; prednisone; cyclophosphamide

INTRODUCTION

A rare cause of a spontaneous, life threatening coagulopathy in adults is the development of immunoglobulin (Ig)G autoantibodies to factor VIII [1]. This ''acquired hemophilia'' can present with bleeding complications at various ages. An unusual cluster of cases recently occurred at our institution which we are reporting. The major portion of their care was in an outpatient setting with an effective oral immunosuppressive regimen.

METHODS AND RESULTS

Seven patients were treated at North Shore University Hospital–NYU School of Medicine, Manhasset, New York during the years 1995 through 1997. These individuals presented with life- or limb-threatening bleeding disorders with no prior history of bleeding complications. All patients were treated with oral cyclophosphamide (100 mg/day) and prednisone (1 mg/kg/day), except for one patient who received only prednisone.

Patient data are listed in the Table I. Comorbid illnesses were many including three patients with coronary artery disease, two patients with diabetes, one patient on oral contraceptive pills, one patient with asthma, one patient with bullous pemphigoid, one patient with hypothyroidism, one patient with renal cell carcinoma, one patient with Addison's disease, one patient with polycythemia vera/myelodysplastic syndrome, and one patient with a history of a lupus anticoagulant.

Laboratory tests revealed a prolonged activated partial thromboplastin time (aPTT) with a normal prothrombin time (PT) and fibrinogen. Tests for disseminated intravascular coagulation (DIC) were negative. The exception was two patients with a prolonged dilute Russell's viper venom time (DRVVT). Mixing studies showed incomplete correction. Incubation of some specimens was required. All patients had decreased factor VIII coagulant activity. Other factor level assays were normal. Bethesda unit assays were done on all patients and were positive for factor VIII antibodies.

Patients were discharged home on oral cyclophosphamide and prednisone after bleeding was stabilized and factor VIII coagulant activity rose. Prednisone and cyclophosphamide were tapered slowly. Patients were followed weekly then monthly as their conditions stabilized.

All patients ultimately achieved complete remission

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TABLE I. Clinical Summary*

Age/ Sex	PTT (sec)	FVIII (sec)	BU	Other	Therapy	Time to CR (weeks)	Duration CR (months)
73/F	52.8	.10	8.0	—	HFVIII PFVIII	4	24+
24/F	72.2	<.01	56	—	PFVIII	10	12+
72/M	73.4	.02	20	DRVVT +	cryoppt FIX	3	10+
74/F	41.8	.14	40	—	PVIII	8	8+
57/M	41.0	.25	22	—	PVIII	3	6+
51/M	44.0	<.02	53	DRVVT +	VCR IVIG PVIII	3	4+
73/M	90.0	<.02	7	DRVVT +	HFVIII PVIII RFVII	8	4+

*PTT, partial thromboplastin time; F, factor; BU, Bethesda unit; CR, complete response; H, human; P, porcine; R, recombinant; DRVVT, dilute Russell's viper venom time; F, factor; VCR, vincristine.

(no detectable inhibitor and normal factor VIII antibody titer). Time to complete remission ranged from 3+ weeks to 3+ months. There did not seem to be any correlation between Bethesda units and time to complete response. Remission durations have been good, with follow-up from 4+ months to 2+ years. One patient relapsed as prednisone and cyclophosphamide were tapered (3+ months after diagnosis), but no significant bleeding occurred at that time and the patient went back into remission as the prednisone and cyclophosphamide were increased.

DISCUSSION

Spontaneous development of autoantibodies to factor VIII is a relatively rare coagulopathy that is classically a disease of older adults. However, as our cases illustrate, it can present with a wide range of severity and varying clinical course. In a study of 65 patients the median age was 62 years (range 18 to 82 years) with an equal male: female ratio and an increasing incidence with age. One third of patients presented with intramuscular bleeding, one fourth with subcutaneous bleeding, and the remainder with hematuria, intraabdominal hemorrhage, or other sites of bleeding. Whereas there were no fatalities in our small series of patients, mortality in general ranges from 15% to 22% [2,3].

In 1994, Green [4] reported early results from a randomized trial that had enrolled 30 patients and used prednisone 1 mg/kg as first line therapy. One third of these patients had restoration of their factor VIII levels with this regimen alone. Nonresponders were randomized to continue prednisone alone, switched to cyclophosphamide, or received the combination. Of these nonresponders, patients who were treated with both cyclophosphamide and prednisone had the highest response rate (50%) [4]. Excellent responses have been reported in which 11 of 12 patients responded after one to three courses of 50–100/kg factor VIII concentrate were given with cyclophosphamide, vincristine, and prednisone every three to four weeks [5].

We believe that our experience is similar to a recent study reported by Shaffer and Phillips [1]. All of our patients had life- or limb-threatening coagulopathies that required immediate and long-term therapy. We also continued to administer immunosuppressive therapy until complete remission was achieved. Our experience was dissimilar in regard to two issues. The first was our observation that there was no correlation between Bethesda unit titers and the severity of the disease. The second was their observation that patients with high antibody titers required the longest therapy. Our experience did not support this.

Our cases demonstrate the wide range of clinical severity that can occur with factor VIII inhibitors. Although most patients are in their sixth or seventh decades, young patients can develop this disease. These cases confirm that immunosuppression with an oral outpatient regimen including cyclophosphamide and prednisone should be the mainstay of therapy.

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